macrocyclic antibiotic interacting with said enantiomers to cause sequential separation by means of more than one of the following mechanisms: complexation, charge-charge interaction, hydrogen bonding, inclusion in a hydrophobic pocket, dipole stacking, or steric interaction, and

(b) recovering the sequentially separated enantiomers as individual enantiomers.--

REMARKS

The instant application is a division of a case which has been allowed and should issue shortly. In the parent application, the claims were directed to a chromatographic process for sequentially separating enantiomers using one of the following macrocyclic antibiotics: glycolpeptides, ansamacrolides and derivatives thereof. The claims were limited to the antibiotics being affixed to a support. In the instant application, a series of claims are presented to cover:

(1) the use of the other macrocyclic antibiotics which are disclosed in the application for sequentially separating enantiomers by chromatography and electrophoresis;

(2) the use of the glycopeptides, ansamacrolides and derivatives thereof for sequential separation of enantiomers by electrophoresis; and

(3) the use of glycopeptides, ansamacrolides and derivatives thereof as mobile phase additives in chromatography (i.e. not bound to a support).

Specifically, the claims currently on file are directed to the following subject matter:

Claims	Subject Matter
1, 5, 6, 9, 10, 15-20	Chromatography and electrophoresis employing macrolides, macrocyclic peptides, polyenes, and derivatives thereof.
21-26	Electrophoresis and chromatography employing aplasmomycin, boromycin, enterobactin, bebeerine and derivatives thereof.
27-28	Electrophoresis employing glycopeptides, ansamacrolides and derivatives thereof.
29	Chromatography employing ansamacrolides and glycopeptides as mobil phase additives.

Thus, as can be seen from the above format, none of the claims in the present invention are the same as the claims in the parent application, but, rather, they claim subject matter which was not claimed in the parent application.

In the grandparent application, the Examiner had relied on DePedro in view of Sitrin and either Konig or Armstrong along with either Hare or Duff to reject the claims. The Examiner had taken the position that DePedro taught the use of macrocyclic antibiotics to separate enantiomers. It should be recalled that applicant's invention, as presently claimed, is directed to the sequential separation of optical isomers or enantiomers. Sequential separation means that both enantiomers are present as a racemic mixture and are separate one from the other. The separation allows for the recovery of both enantiomers as individual enantiomers.

Optical isomers or enantiomers require that the molecule have a chiral center. With respect to amino acids, virtually all amino acids which are derived from proteins and have the L-stereochemical configuration. Recently, it has been discovered that in the cell wall of certain bacteria there is a D-ala-D-ala sequence. The "D" configuration of this amino acid is rare. It is presumed that the bacteria has this "D" sequence to allow it to combat enzymes which destroy bacteria based on the conventional "L" configuration of amino acids which are present in the cell wall of virtually all bacteria. Except for this one case of alanine, virtually all known amino acids obtained from naturally occurring proteins have the same configuration, the "L" configuration and, therefore, there are no racemic mixtures of amino acids obtained from naturally occurring proteins.

Peptides are built from amino acids and comprise two or more amino acids. Because peptides are built from "L" configured amino acids, all peptides have the "L" configuration. There are no naturally occurring racemic mixtures of the peptides. Simply put, racemic mixtures of peptides obtained from naturally occurring proteins do not exist. Although it may be possible to create in a laboratory under artificial conditions a racemic mixture of certain peptides, it would be highly costly and merely an academic exercise.

Proteins are built up from these "L" amino acids, also have only one configuration, the "L" configuration. Thus, like peptides and amino acids obtained from proteins, there are no

racemic mixtures of proteins.

In the article entitled "**Affinity Chromatography of Murein Precursors on Vancomycin-Sepharose**" by DePedro et al., DePedro teaches the use of affinity chromatography to obtain a peptide. It should be appreciated that affinity chromatography does not perform sequential separation. In affinity chromatography, a liquid mixture is brought into contact with a solid support on which a ligand is bound. The ligand attached to one specific component in the mixture and binds that component. All of the other components of the mixture are washed away. Then, a different buffer solution is used in order to break the bonds between the ligand and the retained component so as to release the bound component. Thus, only one component is recovered in an affinity chromatography process. In contrast, the present invention allows for both enantiomers to be recovered because they are sequentially separated.

Currently, there is a need to recover both enantiomers. In the manufacture of a drug, the commercial process typically produces both the "D" and "L" configuration of the drug. Heretofore, patients were given both the "D" and "L" form of the drug. It has recently been discovered that oftentimes it is either the "D" or "L" configuration of the drug that provides the beneficial effect. Typically, it is only <u>one</u> and <u>not both</u> configurations which have a beneficial effect. In fact, in certain cases, it has been found that one configuration is beneficial while the other configuration is harmful. Generally,

drug companies do not know which configuration is beneficial and which configuration is harmful. Thus, there is a need to separate both configurations and to recover both configurations for testing.

It should also be noted with respect to affinity chromatography that affinity chromatography is specific for one component. As a general rule, affinity chromatography only separates one component from solution. The fact that vancomycin separates one type of peptide with a D-ala-D-ala sequence does not lead one of skill in the art to assume it will be useful to separate other peptides let alone separate a wide variety of enantiomers. Applicant's invention is geared towards separating a wide variety of enantiomers.

With respect to the Armstrong and Konig et al. references, both of these references teach the use of cyclodextrin for separating enantiomers. One of skill in the art of separating enantiomers does not consider cyclodextrins to be equivalent to macrocyclic antibiotics such as vancomycin.

It should also be noted that vancomycin bonded to sepharose is unstable. It all likelihood, the material of DePedro will deteriorate after a few hours. It could not stand up to the continuous flow type process such as chromatography.

With respect to Sitrin, Hare and Duff, none of these references teach applicant's presently claimed invention.

Enclosed is a PTO-1449 Form citing references which were cited in the parent case along with copies of each reference.

Respectfully submitted,

BIERMAN, MUSERLIAN AND LUCAS

By Donald Lucas
Donald C. Lucas
Reg. No. 31,275

DCL:pd
Tel. 212-661-8000
Fax. 212-661-8002